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Probabilistic Neighborhood Tractography in the Preterm Neonatal Brain at 3 T

Devasuda Anblagan[1,2], Mark E Bastin[3], Lucy Kershaw[1], Susana Muñoz Maniega[4], Jonathan D Clayden[5], Chinthika Piyasena[6], Graham Wilkinson[7], Neil Roberts[1], Scott I Semple[1], Jane Norman[2], and James P Boardman[2]

[1]Clinical Research Imaging Centre, University of Edinburgh, Edinburgh, United Kingdom, [2]MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom, [3]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom, [4]Brain Research Imaging Centre, University of Edinburgh, Edinburgh, United Kingdom, [5]Institute of Child Health, University College London, London, United Kingdom, [6]BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom, [7]NHS Lothian, Edinburgh, United Kingdom

Introduction/target audience: Preterm birth is a leading cause of cognitive impairment in childhood and is associated with alterations in brain development that are apparent in the neonatal period. Brain structural changes associated with preterm birth include enlargement of the ventricular system, reduced cortical complexity and diffuse white matter signal abnormalities on structural MRI.[1] Diffusion MRI (dMRI) and tractography may provide further insights into the cerebral microstructural changes that accompany preterm birth by supplying quantitative biomarkers of white matter integrity in specific tracts of interest.[2]

Purpose: This pilot work describes the first application of an automatic single seed point tractography-based segmentation method, probabilistic neighborhood tractography (PNT),[3,4] to the study of the preterm brain. PNT, which can segment the same fasciculus across groups of subjects and provide quantitative measures of tract integrity and shape, works by placing seed points in a neighborhood surrounding a seed point transferred from standard space, with the tract that best matches a predefined reference tract in terms of length and shape chosen from this group of 'candidate' tracts.[3]

Methods: Twelve preterm infants with mean postmenstrual age (PMA) 28.43 weeks (range 25.71-30.14) underwent a high angular resolution axial dMRI protocol at term equivalent age (mean PMA 40.28 weeks [range 38-42.56]) without sedation, and with informed parental consent and appropriate ethical approval. The dMRI protocol, acquired using a MAGNETOM Verio 3 T clinical scanner (Siemens AG, Healthcare Sector, Erlangen, Germany), consisted of 11 T2- and 64 diffusion-weighted (b = 750 s/mm^2) single-shot, spin-echo, echo planar imaging volumes acquired with 2 mm isotropic voxels (field of view 256 × 256 mm, imaging matrix 128 × 128, 50 contiguous interleaved slices with 2 mm thickness).

Eight tracts-of-interest were identified using PNT from the dMRI data as implemented in the TractoR package for fiber tracking analysis (http://www.tractor-mri.org.uk).[4] Tracts assessed were the genu and splenium of corpus callosum, cingulum cingulate gyri (CCG), left and right projections of the corticospinal tract (CST), and inferior longitudinal (ILF) fasciculi. Using a 7 × 7 × 7 neighborhood of seed voxels, the seed point which produced the best matching tract to the reference in terms of both length and shape was determined using tract shape models determined from a separate group of normal volunteers aged 25 to 65 years. To reduce false positives and reduce noise-related fall-off in connection probability with distance from the seed point, pruning of streamlines that did not resemble the median path of the best match tract was employed.[4] In a further step, all best match tracts were visually assessed by an experienced rater, and any subject with aberrant or truncated pathways that were not anatomically plausible representations of the fasciculi-of-interest excluded from further analysis. For anatomically acceptable tracts, the resulting tractography masks were applied to each participant's mean diffusivity ($\langle D \rangle$), fractional anisotropy (FA), axial (λ_{Axial}) and radial (λ_{Rad}) diffusivity volumes, which permitted tract-specific mean values of these biomarkers, weighted by the connection probability, to be determined for each tract in every subject. Finally, the absolute goodness-of-fit of the best match tract to the reference (R) for each subject was determined from the log-ratio between the matching likelihood of the chosen candidate tract and the matching likelihood of the reference tract to itself.[3,5] Since the reference tract has, by definition, a log-ratio of zero, this measure of topological similarity will almost always be negative for all other tracts; and the more negative it is, the less good is the fit between the reference and best match tract.

Results: Figure 1 shows the tract segmentation across all 12 subjects for genu and splenium, and indicates the close spatial correspondence of the segmented pathways for these two tracts. Visual assessment of the individual segmented tracts indicated that PNT provided anatomically acceptable representations of the fasciculi of interest for the vast majority of pathways (92 % over all subjects and tracts), with a minimum of 75 % for right CCG.

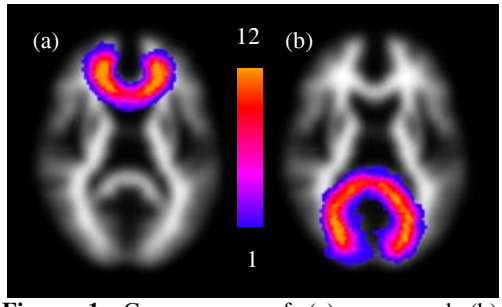

Figure 1. Group maps of (a) genu and (b) splenium generated by transforming the best match tract from each subject into MNI standard space and overlaying them as maximum intensity projections on an MNI white matter volume.

Mean (± SD) values of tract-averaged $\langle D \rangle$, FA, λ_{Axial} and λ_{Rad} for the eight fasciculi of interest are presented in Table 1. Values of $\langle D \rangle$ range from 1139 ± 70 for right CST to 1707 ± 209 μm^2/s for left ILF, while FA ranges from 0.19 ± 0.02 in left ILF to 0.31 ± 0.03 in splenium. Values of λ_{Axial} vary from 1512 ± 76 for right CST to 2061 ± 161 μm^2/s for splenium, while λ_{Rad} ranges from 952 ± 87 for right CST to 1532 ± 200 μm^2/s for left ILF. Finally median (± IQR/2) values of R range from -3.68 ± 0.79 for genu to -47.26 ± 7.45 for left CST and are generally lower, i.e. showing less topological similarity to the reference tract, than those seen in the adult brain.[5]

Discussion/Conclusions: These pilot data show for the first time that quantitative measurements of dMRI biomarkers can be made in the preterm brain from high angular resolution dMRI data using PNT. These values are comparable to other studies using tractography methods and demonstrate the increased diffusivities and reduced FA indicative of white matter development at this point in early life compared with the adult brain.[2] Of particular interest is the fact that the method is able to identify successfully a range of fasciculi using reference tracts obtained from the adult brain. We are currently investigating whether the use of reference tracts from infants further improves this method, and whether the tract shape parameter R provides additional useful information about brain structure that can be used to assess cerebral development in preterm birth and potential therapeutic interventions.

	Acceptable tracts (%)	$\langle D \rangle$ (μm^2/s)	FA	λ_{Axial} (μm^2/s)	λ_{Rad} (μm^2/s)	R
Genu	100	1521 ± 80	0.27 ± 0.05	1973 ± 74	1296 ± 105	-3.68 ± 0.79
Splenium	100	1543 ± 128	0.31 ± 0.03	2061 ± 161	1284 ± 117	-22. 18 ± 4.77
Left CCG	92	1466 ± 236	0.21 ± 0.03	1779 ± 257	1310 ± 227	-11.49 ± 6.21
Right CCG	75	1359 ± 56	0.20 ± 0.02	1643 ± 74	1216 ± 50	-25.54 ± 11.29
Left CST	92	1187 ± 73	0.29 ± 0.03	1562 ± 85	999 ± 75	-47.26 ± 7.45
Right CST	92	1139 ± 70	0.30 ± 0.05	1512 ± 76	952 ± 87	-30.85 ± 6.34
Left ILF	83	1707 ± 209	0.19 ± 0.02	2058 ± 229	1532 ± 200	-11.90 ± 2.37
Right ILF	100	1559 ± 273	0.22 ± 0.03	1924 ± 290	1376 ± 267	-21.00 ± 5.29

Table 1: Mean (± SD) values for tract-averaged $\langle D \rangle$, FA, λ_{Axial} and λ_{Rad} for the eight fasciculi-of-interest. Also shown are median (± IQR/2) values for the absolute goodness-of-fit of the best match tract to the reference (R) and the number of tracts that were considered anatomically plausible representations of each fasciculus.

References: [1] Boardman JP, et al. *Neuroimage* 2010;52:409-414. [2] Thompson DK, et al. *Neuroimage* 2011;55:479-490. [3] Clayden JD, et al. *IEEE Trans Med Imaging* 2007;26:1555-61. [4] Clayden JD, et al. *J Stat Softw*. 2011;44:1-18. [5] Bastin ME, et al. *Neuroimage* 2010;51:1-10. **Acknowledgements:** This work was carried out in collaboration with Siemens Medical Systems. We would like to acknowledge the work of Dr Thorsten Feiweier.